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Original Article

Spontaneous chronic subdural hematoma in elderly people − Arterial hypertension and other risk factors

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Abstract

Background: The risk factors implicated in the genesis of chronic subdural hematomas include old age, alcoholism, diabetes mellitus, arachnoid cysts, coagulopathy, anticoagulant (ACTh) and antiplatelet drugs. However, no study has reported an association between arterial hypertension (HTA) and chronic subdural hematomas. Therefore, the aim of this study was to investigate whether HTA is a risk factor for spontaneous chronic subdural hematomas (SCSDHs).

Methods: This multicenter study included patients aged over 60 years and was conducted from January 2009 to the end of 2015. One hundred and twenty-two patients with SCSDHs and 111 controls treated for other reasons with no evidence of intracranial hemorrhages on brain computed tomography were enrolled. The patients were separated into three age subgroups to provide a better insight into the role of risk factors with age.

Results: The average age in the SCSDH group was 74.45 ± 8.16 years, compared to 71.28 ± 6.69 years in the control group. The SCSDH group was significantly older than the control group ($p = 0.0014$). The patients in the 60−69 years age group diagnosed with SCSDHs had significantly higher rates of HTA ($p = 0.0519$), ACTh treatment ($p = 0.0292$) and alcoholism ($p = 0.0300$) than the control group. The patients in the 70−79 years age group diagnosed with SCSDHs had significantly higher rates of HTA ($p = 0.0071$) and ACTh treatment ($p = 0.0158$) than the control group. In the subgroup of patients older than 80 years, there were no statistical differences.

Conclusion: The incidence of HTA had borderline significance in the patients aged 60−69 years with SCSDHs and statistical significance in the patients aged 70−79 years with SCSDHs. Anticoagulant therapy was the most significant risk factor. Among the patients with SCSDHs aged 60−69 years, the percentage of heavy drinkers was significantly higher than in the control group.

Keywords: Alcoholism; Blood coagulation disorders; Chronic subdural hematoma; Hypertension; Risk factors

1. Introduction

The risk factors commonly associated with the genesis of chronic subdural hematomas (CSDHs) include alcoholism, diabetes mellitus (DM), old age, arachnoid cysts (ACs),[1] coagulopathy, anticoagulant (ACTh), and antiplatelet (APTh) therapy.[2,3] Compared to traumatic hematomas, spontaneous subdural hematomas are often not considered to be a distinct group of hemorrhages when clinical features, therapy, and outcomes are taken into account. The atraumatic nature of this type of bleeding means that potential patients can be identified based on their age, sex and comorbidities. In addition, spontaneous intracranial

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hypotension (induced by cerebrospinal fluid fistula, lumbar puncture, spinal anesthesia,[4] spinal surgery or sudden intracranial decompression) has also frequently been reported to be a cause of CSDHs.

Traumatic CSDHs are defined as bleeding in the subdural space caused by trauma to the head. Such patients present with objective findings (head skin stigmata or with minimal subdural bleeding following the traumatic event on the initial brain computed tomography (CT) scan) or positive anamnesis and/or heteroanamnesis. If neither the patients nor their relatives recall any previous trauma or accident, it should be defined as spontaneous. If the patient denies trauma to the head but members of the family confirm trauma, than it should be considered as traumatic.

No previous study has reported an association between arterial hypertension (HTA) and CSDHs. Therefore, the aim of this study was to investigate whether HTA, in addition to other factors, is a risk factor for spontaneous chronic subdural hematoma (SCSDHs). Moreover, very few studies have investigated the risk factors for atraumatic subdural bleeding. We hypothesized that SCSDHs should be classified as being truly non-traumatic, as the key determinant for the occurrence of CSDHs is sufficient subdural space, that is, cerebral atrophy, and the most common and universal cause of cerebral atrophy is aging.[5] As the geriatric population steadily increases worldwide and as CSDHs are typically a disease of old age, analyzing the risk factors for CSDHs is a matter of global medical interest.

2. Methods

This multicenter study was conducted at two neurosurgical centers from January 2009 to the end of 2015. One hundred and twenty-two patients older than 60 years of age who had been diagnosed with atraumatic SCSDHs were enrolled. None of the patients had any anamnesis or heteroanamnesis data of even minimal head injury in the last 3 months, nor any objective findings of skin stigmata from a recent head injury. The diagnosis of CSDH was confirmed both on preoperative brain CT and intraoperatively. These patients were classified as the SCSDH group.

The prospective control group consisted of 111 randomly selected patients older than 60 years of age who were treated at our institutions for various reasons not related to serious signs and/or symptoms of head injuries. All of these patients had some kind of positive medical history requiring brain CT and/or magnetic resonance imaging (MRI) examinations. None of initial or control (within 3 months) brain CT and/or MRI scans showed any kind of intracranial hemorrhage. Of the control group, 43 patients had a moderate head injury, 32 had some form of benign brain tumor, 14 had symptomatic headaches, 12 had cervical spine injuries, and 10 were tested for an unruptured cerebral aneurysm. While being aware that patients with head injuries have a tendency to develop CSDHs, we decided that CT and/or MRI scans were reliable enough to include the 43 patients with moderate head injuries into the control group. The cervical spine injuries were not associated with any kind of head injury, irrespective of their mechanism of origin. The patients were separated into age groups and tested for statistical differences with regards to the following risk factors: usage of ACTh and APTh therapy, HTA, DM, alcoholism, and the presence of ACs.

Data are presented as mean ± standard deviation, and statistical significance was defined as $p < 0.05$ in all comparisons. Statistical significance was analyzed using the chi-square test for categorical variables and two-sample *t*-tests for continuous variables. The results are presented in tables as numeric values and percentages.

Since the recommended classification was unchanged in the 2003 and 2007 European Society of Hypertension/European Society of Cardiology guidelines, hypertension was defined as systolic blood pressure ≥150 mmHg and/or diastolic blood pressure ≥90 mmHg.[6,7] The patients were defined as having hypertension in this study based on cardiology examinations, previous medical records and therapy, taking into account that we were dealing with an elderly population. The patients with DM were defined according to already extensively published guidelines for the diagnosis and classification of diabetes.[8,9] In brief, we used the current World Health Organization diagnostic criteria for diabetes − fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or 2−h plasma glucose ≥ 11.1 mmol/l (200 mg/dl). Impaired glucose tolerance was not treated as frank diabetes and therefore was not taken into account.

To identify the patients with alcohol addiction, we used the Alcohol Use Disorders Identification Test (AUDIT) to identify those with hazardous and harmful patterns of alcohol consumption.[10,11] Alcoholism was defined on the basis of previous medical records or anamnesis and heteroanamnesis questionnaires where the patients themselves or their relatives described them as heavy drinkers consuming ≥ 14 drinks a week (equivalent to 210 g ethanol) for men or ≥ 9 for women (equivalent to 140 g ethanol).

ACTh drugs included oral anticoagulants such as warfarin, acenocoumarol or the subcutaneous application of heparin (nadroparin-calcium). Some of the patients used a new generation of oral anticoagulants including dabigatraneteksilat and rivaroxaban. The APTh drugs used by the patients in this study included aspirin and clopidogrel. The therapy for each patient was prescribed either by a cardiologist or vascular surgeon. We included only those patients who took any form of the therapy on a regular daily basis. ACs were identified on brain CT and confirmed by a radiologist.

3. Results

3.1. Age and sex

The average age in the SCSDH group was 74.45 ± 8.16 years, compared to 71.28 ± 6.69 years in the control group. The SCSDH group was significantly older than the control group ($p = 0.0014$). There were 87 males and 35 females in

the SCSDH group, and 65 males and 46 females in the control group.

3.2. Arterial hypertension

Overall, 171 of the 233 (75.97%) patients had HTA. Of these patients, 59 (34.50%) did not take antihypertensive therapy prior to hospital admission, and 35 (20.47%) were unaware of this medical problem. The remaining 24 (14.04%) patients did not take any antihypertensive medications despite the recommendations of a physician. One hundred and three (84.40%) patients in the study group had HTA, compared to 68 (61.26%) in the control group.

3.3. Diabetes mellitus

Overall, 56 (24.03%) patients had DM, including 34 (27.87%) in the SCSDH group and 22 (19.81%) in the control group. Of these 56 patients with DM, 48 (85.72%) had type 2 diabetes.

3.4. Anticoagulant therapy

Overall, 44 (18.88%) patients were taking ACThs, including 32 (26.23%) in the SCSDH group and 12 (10.81%) in the control group. In all of the patients that used an older type of ACTh, the international normalized ratio (INR) values were higher than 1.8 on admission, including 16 patients (36.36%) with an INR higher than 3, and three patients (6.82%) with an INR higher than 8.

3.5. Antiplatelet therapy

Overall, 37 (15.88%) patients used APThs, including 22 (18.03%) in the SCSDH group and 15 (13.51%) in the control group. Three patients used a new generation of oral anticoagulant, and five patients used both ACThs and APThs.

3.6. Alcoholism

There were 25 heavy drinkers in this study, or 10.73% of the total 233 patients, including 17 in the study group (16.50%) and eight (7.2%) in the control group. All of the heavy drinkers except one were male.

3.7. Arachnid cysts

All of the ACs were located in the temporal fossa. Two were type I and one was type II.

3.8. Age groups and risk factors

There were 38 patients in the SCSDH group aged from 60 to 69 years, 48 patients aged from 70 to 79 years, 33 patients aged from 80 to 89 years, and three patients older than 90 years. In the control group, there were 53 patients aged from 60 to 69 years, 46 patients aged from 70 to 79 years, 11 patients aged from 80 to 89 years, and one older than 90 years. The distributions of the risk factors for CSDHs in the different age groups are shown in the tables below.

In the 60−69 years age group, ACTh and alcoholism were significantly different compared to the other two analyzed age groups (Table 1). The patients in this age group who had been diagnosed with SCSDHs had significantly higher rates of ACTh therapy ($p = 0.029$) and alcoholism ($p = 0.030$) than the control group. In this group, HTA was borderline significant ($p = 0.052$). In the 70−79 years age group, HTA and anticoagulant therapy were significantly different compared to the other two analyzed groups (Table 2). The patients in this age group who had been diagnosed with SCSDHs had significantly higher rates of HTA ($p = 0.007$) and ACTh therapy ($p = 0.016$) than the control group. In the over 80 years age group, no variables were significantly different compared to the other two analyzed groups (Table 3).

Table 1
Comparisons of comorbidities between the SCSDH and the control groups in the patients aged from 60-69 years.

Risk factors	(N)	HTA*	ACTh**	APTh	DM	Alcoholism***	Arachnoid cyst
SCSDH group	38 (100%)	27 (71.05%)	10 (26.31%)	6 (15.79%)	6 (15.79%)	9 (23.68%)	1 (2.63%)
Control group	53 (100%)	29 (54.72%)	5 (9.43%)	5 (10.87%)	7 (13,21%)	4 (7.55%)	1 (1.89%)
∑	91 (100%)	56 (61.54%)	15 (16.48%)	11 (11.46%)	13 (14.29)	13 (14.29%)	2 (2.08%)

*The chi-square statistic is 3.7803. The p-value is 0.052. This result is borderline significant at $p < 0.05$.
**The chi-square statistic is 4.7552. The p-value is 0.029. This result is significant at $p < 0.05$.
***The chi-square statistic is 4.7066. The p-value is 0.030. This result is significant at $p < 0.05$.

Table 2
Comparisons of comorbidities between the SCSDH and the control groups in the patients aged from 70-79 years.

Risk factors	N	HTA*	ACTh**	APTh	DM	Alcoholism	Arachnoid cyst
SCSDH group	48 (100%)	43 (89.53%)	15 (31.25%)	7 (14.58%)	14 (29.17%)	5 (10.42%)	1 (2.08%)
Control group	46 (100%)	30 (65.22%)	5 (15.21%)	8 (18.60%)	11 (23.91%)	3 (6.52%)	0 (0%)
∑	94 (100%)	73 (77.66%)	20 (21.28%)	15 (15.96%)	25 (26.60%)	8 (8.51%)	1 (1.06%)

*The chi-square statistic is 7.2258. The p-value is 0.007. This result is significant at $p < 0.05$.
**The chi-square statistic is 5.8249. The p-value is 0.016. This result is significant at $p < 0.05$.

Table 3
Comparisons of comorbidities between the SCSDH and the control groups in the patients aged 80 years and over.

Risk factors	N	HTA	ACTh	APTh	DM	Alcoholism	Arachnoid cyst
SCSDH group	36 (100%)	33 (91.67%)	7 (19.44%)	9 (25.00%)	14 (38.89%)	3 (8.33%)	0 (0%)
Control group	12 (100%)	9 (75.00%)	2 (16.66%)	2 (16.67%)	4 (33.00%)	1 (8.33%)	0 (0%)
$\sum$	48 (100%)	42 (87.5%)	9 (18.75%)	11 (22.91%)	18 (37.50%)	4 (8.33%)	0 (0%)

4. Discussion

Chronic subdural hematomas are generally regarded to be a traumatic lesion, and head injury is the most common risk factor, with most patients recalling a head injury or fall.[12] In a large study conducted on 1000 patients, 61.7% stated that they had recently experienced head trauma.[13] The formation of posttraumatic CSDHs has been widely discussed and is generally explained as bleeding after injury of fragile subdural bridging veins rather than in the subarachnoid portion. Traumatic subdural hygromas or laminar acute subdural hematomas seem to be an uncommon alternative stage in the formation of CSDHs.[14]

The formation of SCSDHs has been attributed to forgotten mild trauma of the head or a fall without hitting the head. Coagulopathy[15,16] and other medical procedures[17] have also been associated with the genesis of SCSDHs. SCSDHs have a venous origin of bleeding, and therefore resemble the formation of perimesencephalic (also known as pretruncal) subarachnoid hemorrhages. Both have a venous origin,[18] and therefore have clinically modest manifestations compared to aneurismal subarachnoid hemorrhages or extensive acute subdural hematomas of arterial origin. Canhao et al. reported that hypertension was an independent risk factor for perimesencephalic subarachnoid hemorrhages.[19] Therefore, we hypothesize that hypertension may also be a risk factor for the formation of atraumatic SCSDHs. To the best of our knowledge, no other clinical study has proposed this hypothesis.

All of our patients were older than 60 years, however the SCSDH group was significantly older than the control group. The patients were divided into three subgroups according to age in order to be able to compare age-homogenous comparative subgroups. Our results suggest that hypertension was a significant risk factor for the patients with SCSDHs aged 70–79 years ($p = 0.007$), borderline significant for those aged 60–69 years ($p = 0.052$), but not significant for those over 80 years.

The blood–brain barrier is a highlyselective semipermeable physical barrier that is characterized by specific morphologic and functional properties. It consists of microvascular endothelial cells connected by tight junction proteins, and its purpose is to separate circulating blood from brain extracellular fluid while still allowing intensive cellular transport. It is well known that aging disrupts these processes, resulting in a decline in overall blood–brain barrier function and integrity.[20]

Age-related morphological changes occur at both a tissue and subcellular level, first as a decreased capillary lumen size with increased tortuosity[21] and also as a decrease in parenchyma micro vascularity of the whole brain.[22] A reduced number of mitochondria per endothelial cell then suggests impaired energy-dependent intracellular processes.[20] Functional impairment of the blood–brain barrier presents as inadequate transport of amino acids, hormones, and glucose. Insufficient transbarrier transport in a geriatric population has been shown in vitro,[23] and also in vivo by using positron emission tomography while assessing transport of radiolabeled verapamil.[24]

In patients with a disrupted blood–brain barrier, HTA has been shown to lead to higher intracranial pressure.[25] More than four decades ago, Johnson and Rowan showed that raised intracranial pressure can lead to a higher pressure inside cortical veins.[26] In their study, a close correlation was found between cortical vein pressure and intracranial pressure regardless of the method of raising intracranial pressure (overall correlation coefficient 0.98[26]). Other authors have also reported similar findings regarding the relationship between intracranial pressure and pressure inside cortical veins.[27]

With aging, the mass of the brain decreases, leading to an increase in the space between the brain and the skull ranging from 6% to 11% of the total intracranial space. This causes stretching of the bridging veins which are, therefore, vulnerable and prone to bleeding.[28] When the intravenous pressure inside cortical veins remains high due to unregulated and high arterial pressure, tearing of the stretched veins may occur. The anatomy of the bridging veins predisposes them to tearing within the border cell layer of the dura mater. Thus, the subdural hematoma actually develops within the dura, and then grows by continued bleeding into the border cell layer. The elevation of central venous pressure as the intracranial pressure increases is thought to result from an increase in outflow resistance of the terminal portion of the bridging veins. The increased intracranial pressure then causes further bleeding into the hematoma cavity via the torn bridging veins.[29]

Both anticoagulant therapy and antiplatelet therapy have been significantly associated with an increased risk of CSDHs.[30–32] This association in patients receiving anticoagulant therapy appears to be even stronger in those who develop CSDHs in the absence of recent trauma.[33] Moreover, some authors have reported that using this kind of therapy can precipitate the formation of bilateral CSDHs.[34] In the present study, anticoagulant therapy was the most significant risk factor for the genesis of SCSDHs ($p = 0.029$ for those aged 60–69 years, and $p = 0.016$ for those aged 70–79 years), while there was no statistical significance regarding APTh therapy. A possible reason for the lack of statistical significance may be because the use of the investigated drugs may have been omitted from the medical records of the patients who used APThs, unlike ACThs for which the usage is regularly evidenced in special cards.

Although alcohol problems are often underestimated, drinking seems to be common among the elderly. In a study of community-dwelling persons aged 60−94 years, 62% were found to drink alcohol, and heavy drinking was reported in 13% of men and 2% of women.[35] In the study by Mirand et al.,[35] heavy drinking was defined as having more than 14 drinks per week, as in the current study. Among our SCSDH group, 23.68% were heavy drinkers, compared to 7.55% in the control group ($p = 0.030$). We found no significant difference between the 70−79 and over 80 years age groups with regards to heavy drinking. Interestingly, the percentage of alcoholics was approximately two times lower than in the 60−69 years age group.

Heavy alcohol abuse accelerates brain atrophy, which is a *per se* risk factor for the formation of SCSDHs, and a normal finding in older populations. Shrinkage of the cerebral cortex and white matter, as well as possible atrophy of basal forebrain regions, may result from the neurotoxic effects of alcohol.[36] Some epidemiological and clinical studies have reported an association between heavy drinking and hypertension. However, the mechanism by which alcohol raises blood pressure remains a subject of discussion.[37] Alcohol can also affect both platelet production and function. Thus, heavy drinkers can display a wide spectrum of platelet abnormalities, including impaired platelet aggregation, decreased secretion or activity of the platelet-derived proteins involved in blood clotting, and prolongation of bleeding in the absence of thrombocytopenia.[38]

Although the incidence of DM was higher in all of the SCSDH age subgroups compared to the control group, it did not reach statistical significance. Diabetes mellitus is well known to be associated with morphological changes of arterial macro and microvasculature. Stroke is considered to be a macrovascular complication of DM due to accelerated atherosclerosis of the magistral brain arteries. However, the cerebral microvasculature is also known to be affected by the disease, and the brain has been recognized as a target organ for microvascular complications of DM.[39] Thickening of the cerebral microvascular basement membrane compromises the integrity of adjacent vascular smooth muscle cells, pericytes and astrocytes, along with degeneration of the endothelium.[40] Changes of the microvasculature could play role in the genesis of CSDHs, with regards to the evolution from small laminar initial acute subdural hematomas.

A literature review revealed only a few case reports on the association between ACs and spontaneous[41−43] or posttraumatic chronic subdural hematomas.[44,45] This is consistent with our study, where we only had three cases overall, including two in the 60−69 and one in the 70−79 years age subgroups. These patients had smaller Sylvian fissure cysts (type I and II), and none had type III cysts.[46] Due to the small number of patients with ACs, we could not perform statistical analysis. This is probably owing to the fact that younger, even pediatric patients are more prone to experience this combination.[47]

In conclusion, in this study, the patients with SCSDHs were significantly older than the control group. The incidence of HTA reached borderline significance in the 60−69 years subgroup and statistical significance in the 70−79 years subgroup of patients with SCSDHs. ACTh therapy was the most significant risk factor for the genesis of SCSDHs. Among the patients aged 60−69 years with SCSDHs, the percentage of heavy drinkers was significantly higher than in the control group.

References

1. Shrestha R, You C. Spontaneous chronic subdural hematoma associated with arachnoid cyst in children and young adults. *Asian J Neurosurg* 2014;**9**:168−72.
2. Sim YW, Min K, Lee MS, Kim YG, Kim DH. Recent changes in risk factors of chronic subdural hematoma. *J Korean Neurosurg Soc* 2012;**52**:234−9.
3. Traynelis VC. Chronic subdural haematoma in the elderly. *Clin Geriatr Med* 1991;**7**:583−98.
4. Mashour GA, Schwamm LH, Leffert L. Intracranial subdural hematomas and cerebral herniation after labor epidural with no evidence of dural puncture. *Anesthesiology* 2006;**104**:610−2.
5. Lee KS. Chronic subdural hematoma in the aged, trauma or degeneration? *J Korean Neurosurg Soc* 2016;**59**:1−5.
6. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;**31**:1281−357.
7. Ghaffari S, Pourafkari L, Tajlil A, Sahebihagh MH, Mohammadpoorasl A, Tabrizi JS, et al. The prevalence, awareness and control rate of hypertension among elderly in northwest of Iran. *J Cardiovasc Thorac Res* 2016;**8**:176−82.
8. World Health Organization. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation*. Geneva: World Health Organization; 2006. p. 1−50.
9. Chentli F, Azzoug S, Mahgoun S. Diabetes mellitus in elderly. *Indian J Endocrinol Metab* 2015;**19**:744−52.
10. Thomas F, Babor JC, Higgins-Biddle JB, Saunders MG. *The alcohol use disorders identification test (AUDIT). Guidelines for use in primary care*. The World Health Report. Switzerland, Geneva: World Health Organization; 2001.
11. Piccinelli M, Tessari E, Bortolomasi M, Piasere O, Semenzin M, Garzotto N, et al. Efficacy of the alcohol use disorders identification test as a screening tool for hazardous alcohol intake and related disorders in primary care: a validity study. *BMJ* 1997;**314**:420−4.
12. Jones S, Kafetz K. A prospective study of chronic subdural haematomas in elderly patients. *Age Ageing* 1999;**28**:519−21.
13. Gelabert-González M, Iglesias-Pais M, García-Allut A, Martínez-Rumbo R. Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. *Clin Neurol Neurosurg* 2005;**107**:223−9.
14. Ahn JH, Jun HS, Kim JH, Oh JK, Song JH, Chang IB. Analysis of risk factor for the development of chronic subdural hematoma in patients with traumatic subdural hygroma. *J Korean Neurosurg Soc* 2016;**59**:622−7.
15. Vuk A, Stancić V, Rincić G, Ledinsky M, Grbac L, Stancić N. Non-traumatic bilateral subdural hematoma caused by antiaggregation therapy: case report and review of the literature. *Acta Clin Croat* 2010;**49**:163−8.
16. Bosche B, Molcanyi M, Noll T, Kochanek M, Kraus B, Rieger B, et al. Occurrence and recurrence of spontaneous chronic subdural haematoma is associated with a factor XIII deficiency. *Clin Neurol Neurosurg* 2013;**115**:13−8.
17. Tekin T, Colak A, Kutlay M, Demircan MN. Chronic subdural hematoma after endoscopic third ventriculostomy: a case report and literature review. *Turk Neurosurg* 2012;**22**:119−22.
18. Van der Schaaf IC, Velthuis BK, Gouw A, Rinkel GJE. Venous drainage in perimesencephalic hemorrhage. *Stroke* 2004;**35**:1614−8.
19. Canhao P, Falcao F, Pinho E, Melo T, Ferro J, Ferro H. Vascular risk factors for perimesencephalic nonaneurysmal subarachnoid hemorrhage. *J Neurol* 1999;**246**:492−6.

20. Zeevi N, Pachter J, McCullough LD, Wolfson L, Kuchel GA. The blood-brain barrier: geriatric relevance of a critical brain-body interface. *J Am Geriatr Soc* 2010;**58**:1749−57.
21. Shah GN, Mooradian AD. Age-related changes in the blood-brain barrier. *Exp Gerontol* 1997;**32**:501−19.
22. Brown WR, Moody DM, Thore CR, Anstrom JA, Challa VR. Microvascular changes in the white mater in dementia. *J Neurol Sci* 2009;**283**: 28−31.
23. Mooradian AD. Potential mechanisms of the age-related changes in the blood-brain barrier. *Neurobiol Aging* 1994;**15**:751−5.
24. Toornvliet R, van Berckel BN, Luurtsema G, et al. Effect of age on functional P-glycoprotein in the blood-brain barrier measured by use of (R)-[(11)C] verapamil and positron emission tomography. *Clin Pharmacol Ther* 2006;**79**:540−8.
25. Kongstad L, Grände PO. Arterial hypertension increases intracranial pressure in a cat after opening of the blood-brain barrier. *J Trauma* 2001; **51**:490−6.
26. Johnston IH, Rowan JO. Raised intracranial pressure and cerebral blood flow. 3. Venous outflow tract pressures and vascular resistances in experimental intracranial hypertension. *J Neurol Neurosurg Psychiatry* 1974;**37**:392−402.
27. Nakagawa Y, Tsuru M, Yada K. Circulatory disturbance of the venous system under intracranial hypertension−pressure gradient of the venous pathways between cortical vein and superior sagittal sinus. *No Shinkei Gek* 1974;**2**:39−45.
28. Ellis GL. Subdural haematoma in the elderly. *Emerg Med Clin North Am* 1990;**8**:281−94.
29. Miller JD, Nader R. Acute subdural hematoma from bridging vein rupture: a potential mechanism for growth. *J Neurosurg* 2014;**120**: 1378−84.
30. Hart RG, Boop BS, Anderson DC. Oral anticoagulants and intracranial hemorrhage. Facts and hypotheses. *Stroke* 1995;**26**:1471−7.
31. Baechli H, Nordmann A, Bucher HC, Gratzl O. Demographics and prevalent risk factors of chronic subdural haematoma: results of a large single-center cohort study. *Neurosurg* 2004;**27**:263−6.
32. Lindvall P, Koskinen LO. Anticoagulants and antiplatelet agents and the risk of development and recurrence of chronic subdural haematomas. *J Clin Neurosc* 2009;**16**:1287−90.
33. De Bonis P, Trevisi G, de Waure C, Sferrazza A, Volpe M, Pompucci A, et al. Antiplatelet/anticoagulant agents and chronic subdural hematoma in the elderly. *PLoS One* 2013;**8**:e68732.
34. Tsai TH, Lieu AS, Hwang SL, Huang TY, Hwang YF. A comparative study of the patients with bilateral or unilateral chronic subdural hematoma: precipitating factors and postoperative outcomes. *J Trauma* 2010; **68**:571−5.
35. Mirand AL, Welte JW. Alcohol consumption among the elderly in a general population, Erie County, New York. *Am J Public Health* 1996;**86**: 978−84.
36. Lishman WA. Alcohol and the brain. *Br J Psychiatry* 1990;**156**:635−44.
37. Husain K, Ansari RA, Ferder L. Alcohol-induced hypertension: mechanism and prevention. *World J Cardiol* 2014;**6**:245−52.
38. Ballard HS. Hematological complications of alcoholism. *Alcohol Clin Exp Res* 1989;**13**:706−20.
39. Bohlen HG, Niggl BA. Adult microvascular disturbances as a result of juvenile onset diabetes in Db/Db mice. *Blood Ves* 1979;**16**:269−76.
40. Moore SA, Bohlen HG, Miller BG, Evan AP. Cellular and vessel wall morphology of cerebral cortical arterioles after short-term diabetes in adult rats. *Blood Ves* 1985;**22**:265−77.
41. Hong JC, Kim MS, Chang CH, Kim SH. Arachnoid cyst with spontaneous intracystic hemorrhage and chronic subdural hematoma. *J Korean Neurosurg Soc* 2008;**43**:54−6.
42. Patel AP, Oliverio PJ, Kurtom KH, Roberti F. Spontaneous subdural hematoma and intracystic hemorrhage in an arachnoid cyst. *Radiol Case Rep* 2009;**4**:298.
43. Parsch CS, Krauss J, Hofmann E, Meixensberger J, Roosen K. Arachnoid cysts associated with subdural hematomas and hygromas: analysis of 16 cases, long-term follow-up, and review of the literature. *Neurosurgery* 1997;**40**:483−90.
44. Donaldson JW, Edwards-Brown M, Luerssen TG. Arachnoid cyst rupture with concurrent subdural hygroma. *Pediatr Neurosurg* 2000;**32**:137−9.
45. Tsitsopoulos PP, Pantazis GC, Syrmou EC, Tsitsopoulos PD. Intracranial arachnoid cyst associated with traumatic intracystic hemorrhage and subdural haematoma. *Hippokratia* 2008;**12**:53−5.
46. Galassi E, Tognetti F, Gaist G, Fagioli L, Frank F, Frank G. CT scan and metrizamide CT cisternography in arachnoid cysts of the middle cranial fossa: classification and pathophysiological aspects. *Surg Neurol* 1982;**17**: 363−9.
47. Mori K, Yamamoto T, Horinaka N, Maeda M. Arachnoid cyst is a risk factor for chronic subdural hematoma in juveniles: twelve cases of chronic subdural hematoma associated with arachnoid cyst. *J Neurotrauma* 2002; **19**:1017−27.